

Chapter 2

Results: Developments of New Radical Cascades with *N*-Acylcyanamides

2.1 Objectives of the Project

Since radical cascades using cyanamides have been reported only starting from aryl radicals, we have wished to broaden the scope of these cascades. Our objectives were to test the reactivity of alkyl, vinyl and aminyl radicals in this process. Indeed, the use of alkyl and vinyl radical should provide us with a straightforward access to natural and biologically active quinazolinones; while the use of aminyl radicals should afford the first radical synthesis of guanidines (Fig. 2.1).

2.2 Addition of Alkyl Radicals

We first examined the possibility to engage alkyl radicals in cascades with *N*-acylcyanamides. We wished to explore the scope of the reactivity, by varying the substitution of the alkyl radical and the length of the arm that will determine the size of the first ring formed.

2.2.1 Synthetic Targets

Four synthetic targets were defined (Fig. 2.2), with two of them being natural quinazolinones.

Deoxyvasicinone is a natural alkaloid which was isolated in 1957 from the leaves of *Adhatoda vasica* [1]. This compound possesses anti-depressive, anti-bacterial and anti-inflammatory properties [2]. A wide variety of methodologies have been reported for its synthesis via pallado-catalyzed tandem carbonylation/cyclization [3], transition metal complex-catalyzed reductive *N*-heterocyclization [4] or tandem intramolecular Staudinger/aza-Wittig reactions [5]. In 2007,

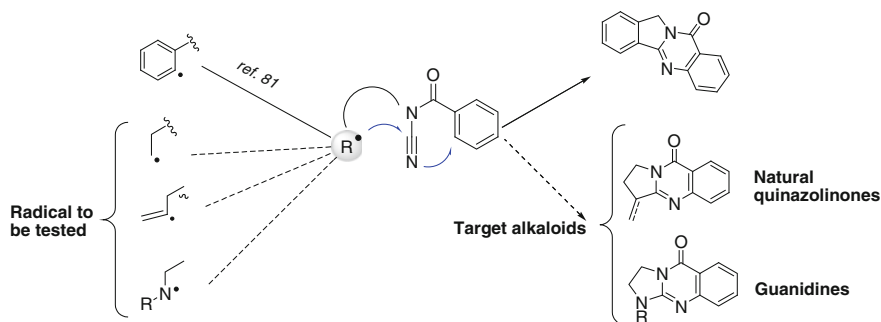


Fig. 2.1 Objectives of the new radical cascades with cyanamides

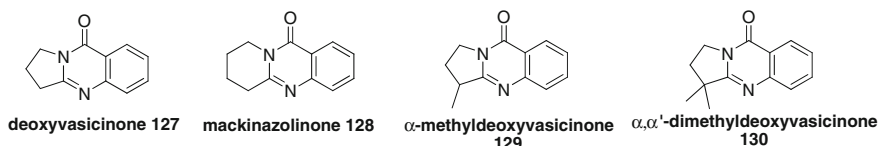
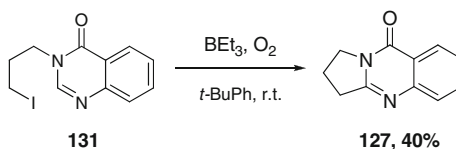


Fig. 2.2 Synthetic targets

Fig. 2.3 Bowman's radical synthesis of deoxyvasicinone



Bowman has reported the first radical synthesis of deoxyvasicinone [6]. Treatment of alkyl iodide **131** with BEt_3 and O_2 allowed the generation of the corresponding alkyl radical and its oxidative cyclization on 3*H*-quinazolin-4-one core (Fig. 2.3).

Mackinazolinone **128** is a natural quinazolinone fused with a piperidine ring. This compound was isolated in 1965 in New Guinea from the leaves of *Mackinlaya subulata* [7] and has demonstrated a large spectra of pharmaceutical activities [8, 9]. Numerous synthetic methodologies similar to those developed for deoxyvasicinone have been applied to the building of mackinazolinone, including Bowman's radical cyclization [5, 6].

α -Methyldeoxyvasicinone **129** is an unnatural analogue of deoxyvasicinone presenting bronchodilator activities [10]. Six syntheses of this compound have been reported, none of them presenting a radical step [11]. α, α' -Dimethyldeoxyvasicinone **130** has never been described.

2.2.2 Synthesis of Cascade Precursors

2.2.2.1 *N*-Acylcyanamide Precursors for Deoxyvasicinone and Mackinazolinone

The synthesis of the desired cyclization precursors was devised according to the retrosynthetic scheme in Fig. 2.4. *N*-Acylcyanamides **132** could be obtained by cyanation of corresponding amides **133** which would derive from acylation of corresponding amines **134**.

Our first idea was to synthesize bromo precursors for the cyclization (Fig. 2.4, X = Br). However, when commercial 3-bromopropylamine hydrobromide **135** was treated with triethylamine and benzoyl chloride, only 28 % of the desired amide **136** was obtained (Fig. 2.5). The major product **137** resulted from an intramolecular O-alkylation side-reaction.

We have consequently substituted the bromine with a phenylselenium group which is known as a good radical leaving group but a poor nucleofuge (Fig. 2.4, X = SePh). 3-Bromopropylamine hydrobromide **135** and 4-bromobutylamine hydrobromide **138** (obtained by treatment of commercial 4-aminobutan-1-ol with HBr as a 48 % aqueous solution) [12] were converted to their seleno derivatives by reaction with diphenyldiselenide and sodium borohydride [13]. Benzoylation of the amino groups were then efficiently performed, affording seleno amides **133a** and **133b** in good yields. Cyanation of the amides under the reaction conditions described for the aryl substrates [14] (3 equivalents of cyanogen bromide and 1 equivalent of sodium hydride) led to disappointing yields of the corresponding *N*-acylcyanamides (20 %). However, switching from sodium hydride to potassium hydride proved very beneficial for the reaction, probably thanks to the formation of a more nucleophilic potassium salt intermediate. With optimum cyanation

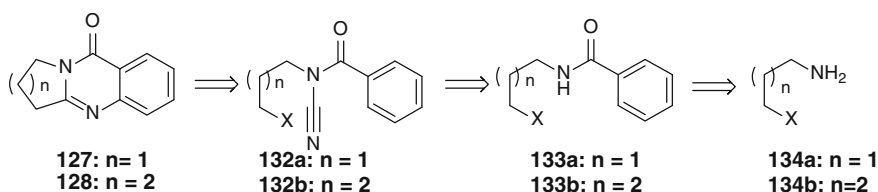


Fig. 2.4 Retrosynthetic scheme

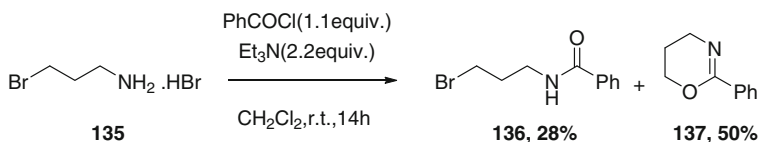


Fig. 2.5 Attempt to perform direct benzoylation of bromoamine

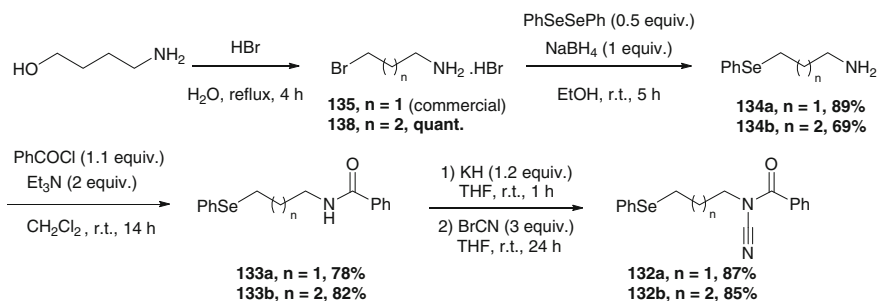


Fig. 2.6 Synthesis of unsubstituted cyclization precursors

conditions in hands (3 equivalents of cyanogen bromide and 1.2 equivalents of potassium hydride), we could obtain the desired *N*-acylcyanamides **132a** and **132b** in more than 85 % yields (Fig. 2.6).

2.2.2.2 *N*-Acylcyanamide Precursor for α -methyldeoxyvasicinone

N-Acylcyanamide precursor **145** for α -methyldeoxyvasicinone was synthesized in six steps from commercially available 1,3-dichlorobutane **139** (Fig. 2.7). Selective monoiodination by Finkelstein reaction afforded 3-chloro-1-iodobutane **140**, which was reacted with potassium phthalimide to provide compound **141**. Conversion of the secondary chloride to phenyl selenium group was achieved by treatment with in situ generated sodium phenylselenoate. Deprotection of the phthalimide group with hydrazine afforded selenoamine **143**. The amine was first

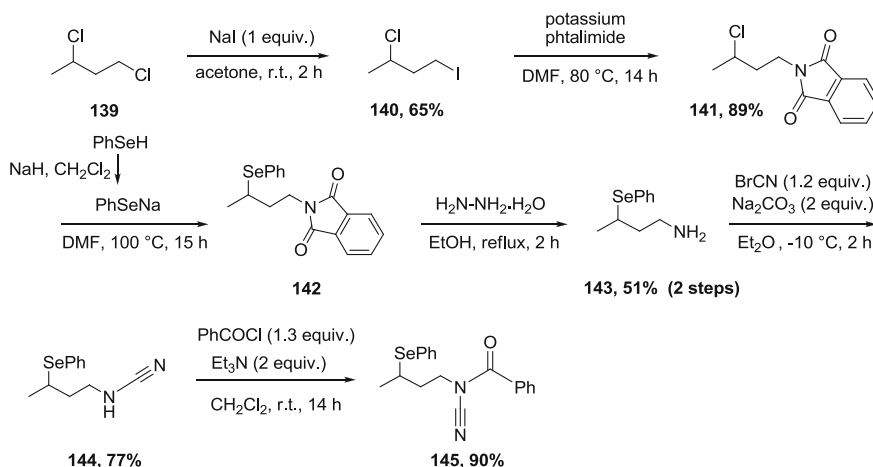


Fig. 2.7 Synthesis of α -methyldeoxyvasicinone precursor

converted into the corresponding cyanamide **144** according to Harrison's methodology, [15] then acylated to obtain the desired *N*-acylcyanamide **145** in satisfying yield.

2.2.2.3 *N*-Acylcyanamide Precursor for α,α' -methyldeoxyvasicinone

The *N*-acylcyanamide precursor for α,α' -methyldeoxyvasicinone was the most challenging to prepare. Its synthesis was carried out in six steps starting from commercially available 3,3-dimethylallyl bromide **146**. Heating **146** with potassium phthalimide at 80 °C led to the desired phthalimide derivative **147**. Hydrobromination of the double bond was then performed by treatment with HBr solution in acetic acid (Fig. 2.8).

Several conditions were tested to displace the tertiary bromide of **148** with phenylselenium. The only successful strategy was the indium mediated procedure developed by Jang et al. [16]. The key feature of this methodology is the reduction of the alkylbromide by indium metal to generate the corresponding alkyl radical **150**. This latter can then perform a homolytic substitution at the selenium atom of diphenyldiselenide to afford selenoester **152** (Fig. 2.9).

Finally, treatment of phthalimide **152** with hydrazine afforded the free amine **153**. For purification issues, the amine was first acylated then cyanated leading in two steps to the desired *N*-acylcyanamide **155** (Fig. 2.10).

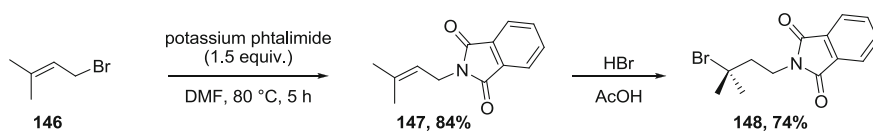


Fig. 2.8 Synthesis of intermediate bromophthalimide **148**

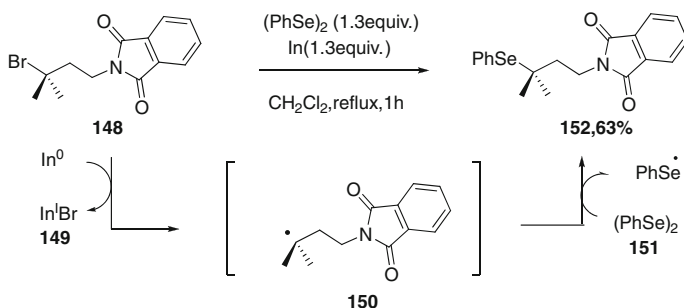


Fig. 2.9 Conversion of tertiary bromide to alkyl phenyl selenide

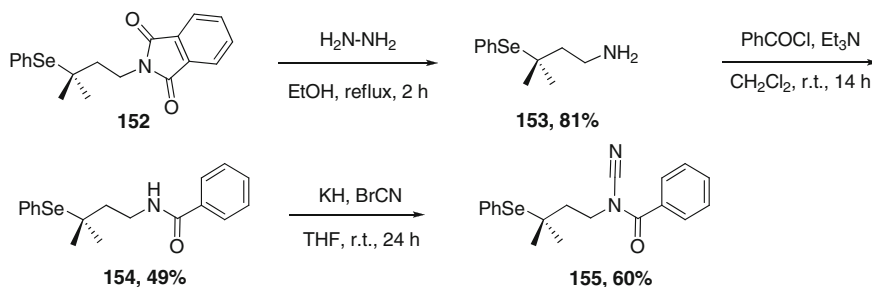


Fig. 2.10 Synthesis of *N*-acylcyanamide precursor for α,α' -methyldeoxyvasicinone

2.2.3 Radical Cyclization of the *N*-acylcyanamide Precursors

The four *N*-acylcyanamide precursors were then reacted under the reaction conditions that were previously developed in the laboratory for the cyclization of alkyl phenylselenoates [17]. Cyclization proceeded smoothly in all cases, under slow addition of Bu_3SnH (1.2 equivalents) and AIBN (1.5 equivalents) in refluxing benzene (0.017 M). The major tin derivative formed during the reaction is Bu_3SnSePh , which is stable on silica gel and non-polar. The purification of quinazolinones was facilitated by their high polarity. A first washing of the column chromatography with pentane eliminated the tin residues, and subsequent elution with polar solvents allowed the isolation of pure products (Fig. 2.11).

Under those conditions, deoxyvasicinone **127** was isolated in 65 % yield. We attempted to replace the tin mediator with $(\text{TMS})_3\text{SiH}$, however the yield dropped to only 20 %. Chatgililoglu's reagent is yet known to react with alkyl phenylselenates readily [18], but proved not adapted to our cascade. Cyclization of precursor **132b** allowed the isolation of mackinazolinone **128** in 51 % yield along with the product of direct reduction. This result could be explained by the lower kinetic constant of 6-*exo-dig* cyclization compared to 5-*exo-dig*. However, the successful isolation of mackinazolinone was the first evidence that the cascade could begin not only with 5-*exo-dig* cyclization but also 6-*exo-dig* processes.

α -Methyldeoxyvasicinone **129** and α,α' -dimethyldeoxyvasicinone **130** were obtained in good 76 and 87 % yields respectively. The trend observed with these few examples seems to show that the more nucleophile is the first radical formed, the more efficient is the cyclization. Thus, it appears that cyclization on the cyanamide moiety could be favored with nucleophilic radicals, which evidences that *N*-acylcyanamides are electrophilic acceptors.

To conclude, this project allowed us to demonstrate that alkyl radicals could take part easily in radical cascades with *N*-acylcyanamides [19]. The size of the first ring formed and the substitution of the radical could be varied, and three biologically active products have been synthesized along with non-reported analogue α,α' -dimethyldeoxyvasicinone, whose activity should be tested. A new range of quinazolinone type products should be now available by using our

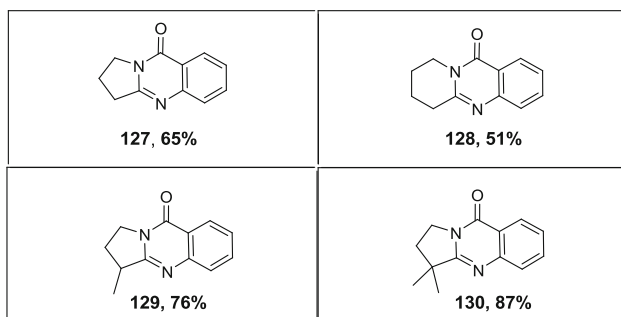
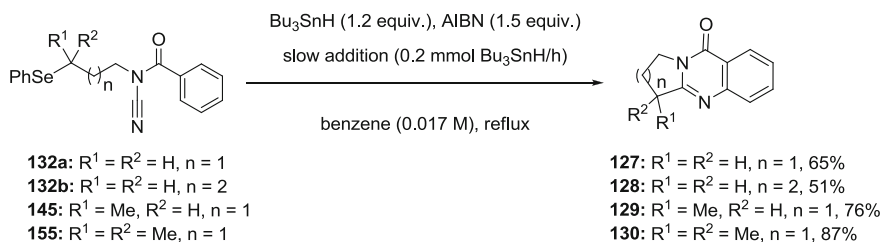


Fig. 2.11 Radical cyclization of *N*-acylcyanamides

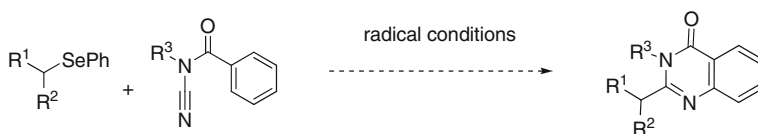


Fig. 2.12 Envisaged intermolecular version of the cascade

methodology. A perspective to broaden again the scope of products would be to develop an intermolecular version as depicted in Fig. 2.12. This strategy should furthermore simplify the synthesis of the precursors, which can be fastidious for intramolecular reactions.

2.3 Addition of Vinyl Radicals to *N*-acylcyanamides

Stimulated by the good reactivity of alkyl radicals with cyanamides, we next turned our attention towards the behavior of vinyl radicals. Our first idea was to synthesize the core of natural alkaloid isaindigotone **156** [20, 21], which possesses interesting antioxidant properties. We proposed that isaindigotone could be constructed via a Heck reaction on key intermediate **157**, obtained by cascade cyclization of *N*-acylcyanamide precursor **158** (Fig. 2.13).

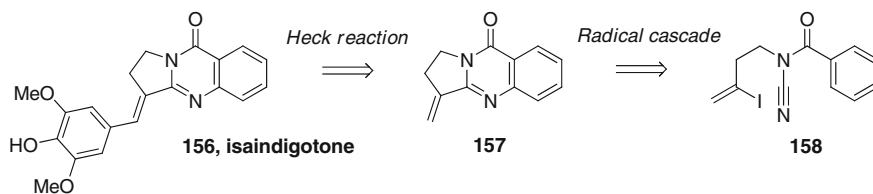


Fig. 2.13 Retrosynthetic plan for the synthesis of isaindigotone

2.3.1 Radical Cyclization of Vinyliodide Precursor Followed by an Unexpected Reduction

2.3.1.1 Synthesis of the Precursor

3-Iodo-but-3-enylamine **161** was first synthesized from 3-butyn-1-ol **159** according to the methodology described by Sugiyama et al. [22]. Regioselective hydroiodination was achieved using sodium iodide, trimethylsilylchloride and water. Subsequent tosylation of the hydroxyl group afforded tosylate **160** which was substituted with sodium azide. Staudinger reduction of the azide function finally yielded the desired amine **161** (Fig. 2.14).

Owing to the volatility of amine **161**, we first planned to install the *N*-acyl cyanamide function by benzoylation followed by cyanation (Fig. 2.15). However, when amide **162** was treated with potassium hydride and cyanogen bromide, we observed the addition of BrCN to the double bond, delivering amide **163**. Indeed, examples of addition of BrCN on furans [23], alkenes [24] and alkynes have been previously reported in the literature [25].

We wondered whether inverting the order of the sequence, hence performing first the cyanation on the primary amine then the acylation, could be beneficial for the outcome of the reaction. Indeed, we hoped that the higher nucleophilicity of the amine compared to the amide would allow it to react faster with BrCN than the

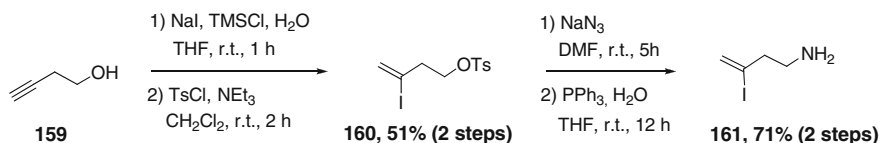


Fig. 2.14 Synthesis of 3-iodo-but-3-enylamine

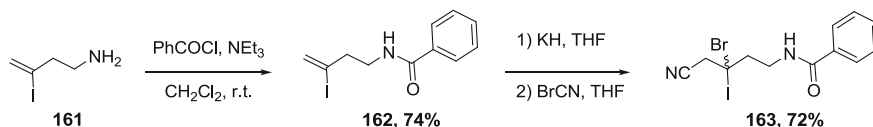


Fig. 2.15 First attempt to install the *N*-acylcyanamide function

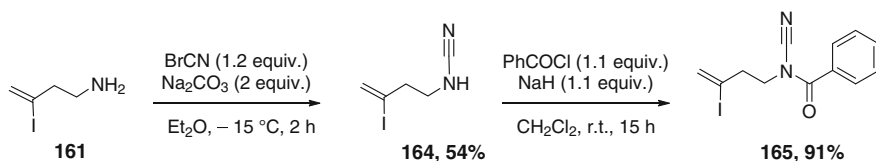


Fig. 2.16 Inversion of the sequence to obtain the *N*-acylcyanamide

alkene. This idea proved valuable, since the inversion of the sequence allowed us to obtain the desired *N*-acylcyanamide **165**. Intermediate cyanamide **164** could be isolated; however it proved quite unstable under air and had to be engaged in the next step immediately (Fig. 2.16).

2.3.1.2 Radical Cyclization

With the desired precursor **165** in hand, we submitted it to the radical cyclization conditions developed for aryl iodides [14]. Under treatment with Bu₃SnH (2 equivalents) and AIBN (1.5 equivalents) slowly added in refluxing benzene, we obtained the desired cyclization, but to our great surprise, in the major product **129** the exocyclic double bond had been fully reduced during the cascade. In the minor product **167**, the double bond had not been reduced but had migrated to an endocyclic position (Fig. 2.17).

After this surprising result, the influence of different parameters on the outcome of the reaction was tested (Fig. 2.18). Running the reaction in boiling toluene led to **129** (59 %) and **167** (15 %), with the apparition of side-product of direct reduction **166** (18 %) (entry 2). The use of *tert*-butanol gave exclusively product **129** in the highest isolated yield (77 %) (entry 3). Following this solvent screening, the amount of initiator was gradually lowered (entries 4-6). The NMR yield of **129** slightly decreased from 79 to 72 %, 64 and 57 % when the loading of AIBN was 1.5 equiv., 1 equiv., 0.5 equiv. and 0.25 equiv. respectively. This shows that the formation of **129** does not require a stoichiometric amount of AIBN and likely steams from a radical chain mechanism. However, the propagation of the chain may be of weak efficiency since below 1 equiv. of AIBN some byproducts as well as starting material were recovered.

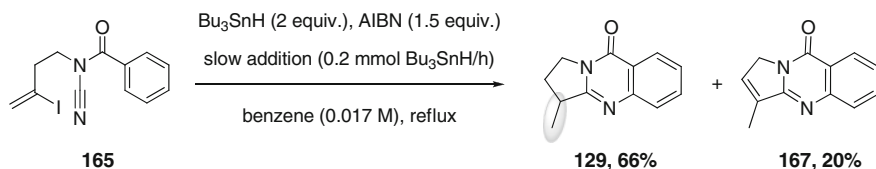
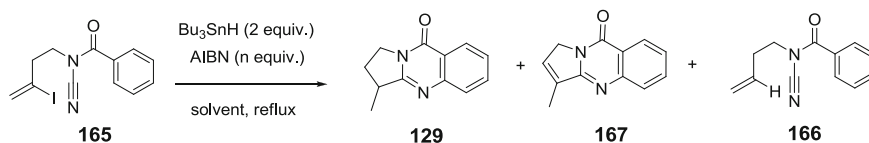


Fig. 2.17 Radical cyclization of vinyl iodide precursor



Entry	Solvent	n	Yield 129 [%]	Yield 167 [%]	Yield 166 [%]	SM [%]
1	benzene	1.5	66	20	<5%	<5%
2	toluene	1.5	59 ^a	15	18	<5%
3	<i>t</i> -BuOH	1.5	77 (79) ^a	12	<5%	<5%
4	<i>t</i> -BuOH	1	72 ^a	13	<5%	<5%
5	<i>t</i> -BuOH	0.5	64 ^a	11	13%	<5%
6	<i>t</i> -BuOH	0.25	57 ^a	10	8%	6%

[a] NMR yields (butadiene sulfone used as internal standard)

Fig. 2.18 Influence of solvent and AIBN loading

2.3.2 Mechanistic Studies

2.3.2.1 Origin of Both Novel Hydrogens

In order to understand the formation of product **129**, we wished first to investigate the origin of both hydrogens causing the reduction of the *exo* double bond. For that purpose, we primarily treated vinyl iodide precursor **165** with tributyltin deuteride (Fig. 2.19). Quinazolinone **169** with a deuterium atom on the five-membered ring was isolated, demonstrating that the hydrogen at this position came from the tin mediator.

In a second time, we prepared vinyl iodide precursor **170** bearing a *penta*-deuterated benzoyl ring, in a similar fashion to precursor **165** using *d*₅-benzoyl chloride in the last step (see SI). We then made react deuterated precursor **170** under the usual radical cyclization conditions. We obtained quinazolinone **171** bearing a deuterium on the methyl group. That result taught us that the hydrogen at that position had migrated from the benzoyl ring (Fig. 2.20).

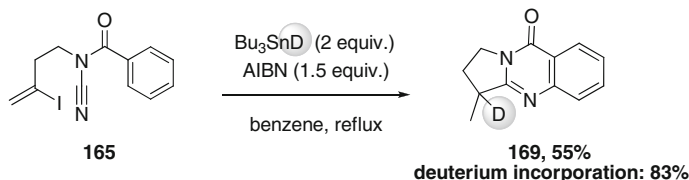


Fig. 2.19 Origin of the internal hydrogen

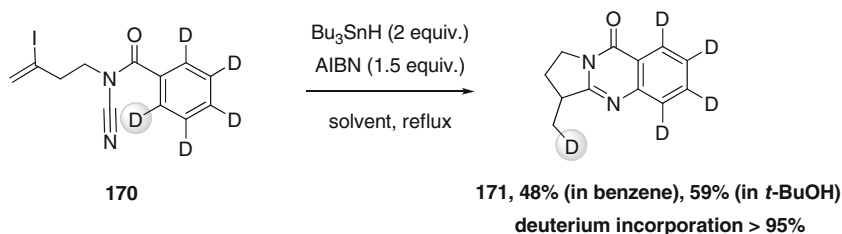


Fig. 2.20 Origin of the external hydrogen

2.3.2.2 Discrimination Between an Intra- and an Intermolecular Mechanism

In order to discriminate between an intra- and an intermolecular migration of hydrogen, we imagined to perform a double tagging experiment, with 0.5 equivalent of a precursor bearing a *penta*-deuterated benzoyl ring and 0.5 equivalent of a precursor bearing hydrogens on its benzoyl ring. To facilitate the separation on silica gel chromatography of the cyclized products, we chose to use precursor **172** bearing a polar *para*-methoxy substituent as a test precursor. Vinyl iodide **172** was synthesized as reported in Fig. 2.21, and cyclized under the usual conditions, leading to reduced quinazolinone **173** in 72 % yield.

We then mixed 0.5 equivalent of precursor **170** and 0.5 equivalent of precursor **172** and analyzed the outcome of the cyclization. Four products were isolated (**174** was isolated in mixture with **173** and **175** in mixture with **171**), demonstrating that the hydrogen migration was intermolecular. Indeed, if the mechanism had been intramolecular, **172** would have led to all-hydrogen product **173** only and **170** to all-deuterium product **171** only. The formation of the four products attests that the two precursors have exchanged hydrogen (or deuterium) between one another (Fig. 2.22).

Since hydrogen seemed to migrate in an intermolecular fashion, we attempted to trap it before its addition on the external position of quinazolinone. For that purpose, we introduced in the reaction mixture 5 equivalents of a very good radical acceptor, benzylidene malonitrile **176**. We expected that it would play the role of a sacrificial acceptor (Fig. 2.23). Indeed, the presence of benzylidene malonitrile successfully inhibited the formation of reduced quinazolinone **129**, providing instead adduct **177**. Compound **177** could arise from the addition of hydrogen to

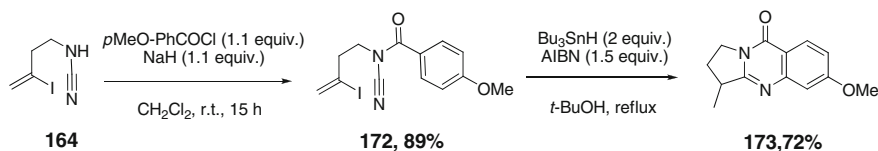


Fig. 2.21 Synthesis and cyclization of *p*-methoxy substituted precursor

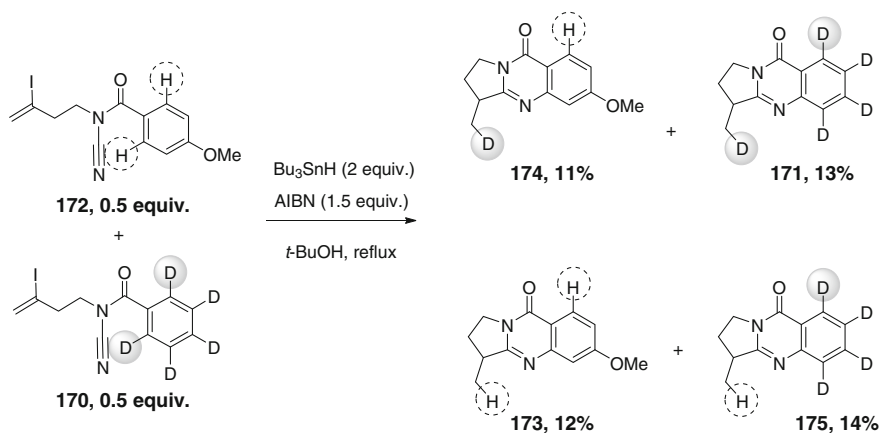
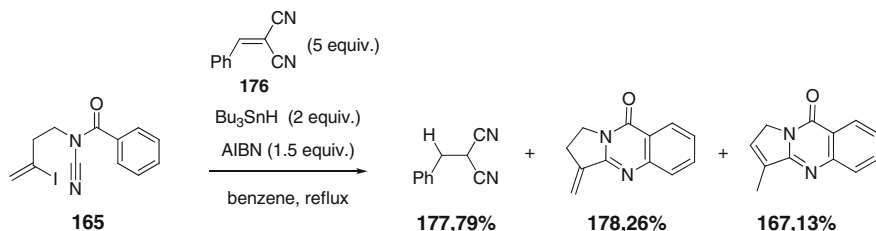


Fig. 2.22 Double tagging experiment

Fig. 2.23 Trapping of the $\text{H}^\bullet$ with a sacrificial acceptor

benzylidene malonitrile followed by radical termination by transfer of second hydrogen from Bu_3SnH . However, the exomethylene product **178** proved very unstable under the reaction conditions, and was consequently isolated in a disappointing 26 % yield, along with endomethylene product **167**.

In order to ascertain that the sacrificial acceptor had intercepted hydrogen coming from the benzoyl ring of *N*-acylcyanamide precursor, deuterated precursor **170** was reacted under the same reaction conditions. The outcome was very similar and in accordance with our assumption, delivering adduct **179** with a deuterium incorporation of 74 % (Fig. 2.24).

2.3.2.3 Influence of Steric Hindrance

We first wished to assess the influence of steric hindrance at the *exo* methylene on the output of the reaction. Indeed, in the case of a bimolecular approach, the migration of hydrogen should be sensitive to hindrance at the double bond. We envisaged synthesizing precursor **182**, bearing a trisubstituted double bond starting

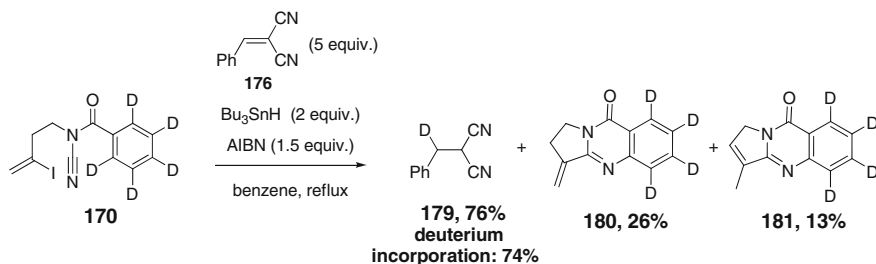
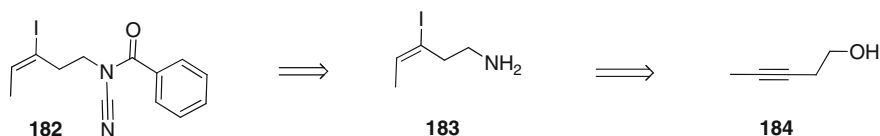
Fig. 2.24 Trapping of $D^\bullet$ with a sacrificial acceptor

Fig. 2.25 Retrosynthetic plan for the synthesis of methyl substituted vinylidide

from corresponding alkynol **184**, with a similar strategy to that employed for simple precursor **165** (Fig. 2.25).

The synthesis started under unfavorable auspices, since treatment of alkynol **184** with NaI, TMSCl and H_2O led to an unseparable mixture of two regioisomers **185** and **186** in a 1.5/1 ratio (Fig. 2.26). The methyl substituent on the alkyne had strikingly lowered the regioselectivity of the hydroiodination. Since the amount of product engaged was not negligible, we decided to carry on the reactions with the regioisomer mixture, in the hope of being able to separate them later in the synthesis. We thus tosylated the hydroxyl functions, and obtained an unseparable

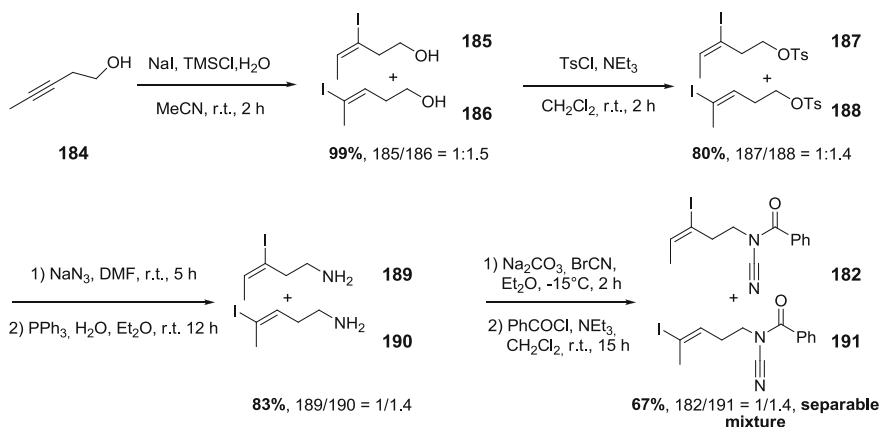


Fig. 2.26 Synthesis of the methyl substituted precursor and its regioisomer

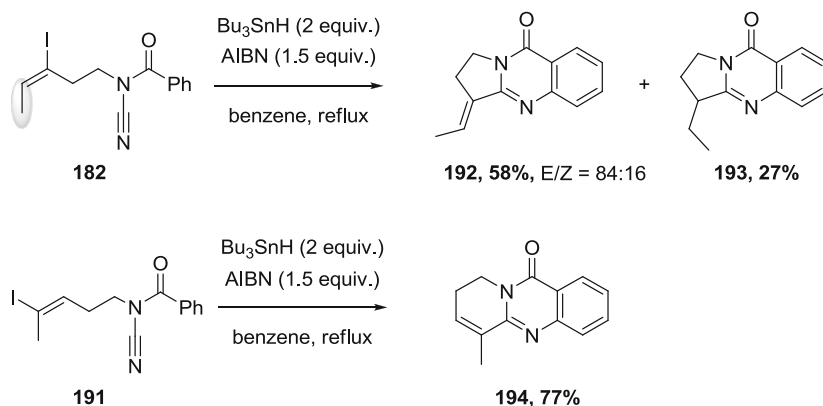


Fig. 2.27 Radical cyclization of precursors bearing a trisubstituted double bond

mixture of tosyls **187** and **188**. Nucleophilic substitution with sodium azide followed by Staudinger reduction afforded unseparable amines **189** and **190** that were submitted to cyanation and subsequent acylation in the previously employed conditions. To our great delight the *N*-acylcyanamides formed could, at last, be separated by flash column chromatography, delivering two cyclization precursors (instead of one!) **182** and **191**.

Both new *N*-acylcyanamides **182** and **191** possessing a trisubstituted double bond were cyclized under the usual radical conditions. Cyclization of **182** led to quinazolinone **192** still bearing the double bond as a major product (58 %) (Fig. 2.27). Reduced quinazolinone **193** was only isolated in 27 % yield. The presence of a methyl substituent at the double bond thus seemed to block the H migration process.

The cyclization of precursor **191** confirmed that when the double bond was *endo*, it could not be affected by H migration. Indeed, the reduction of the double bond was completely inhibited and quinazolinone **194** was isolated as the sole product.

Additionally, the cyclized product **192** bearing a trisubstituted double bond showed a higher stability under our radical conditions. Thus, cyclization of precursor **182** in the presence of 5 equivalents of benzylidene malonitrile led in a high 92 % yield to quinazolinone **192** (Fig. 2.28).

In a second time, we wished to assess the influence of steric hindrance at the *meta* position of the benzoyl ring on the outcome of the cascade reaction. We synthesized precursor **195** bearing *meta* methyl substituents and precursor **196** *meta tert*-butyl substituents. The presence of methyl substituents appeared to have little influence on the cascade process, since reduced quinazolinone **197** was isolated as the sole product in 63 % yield (Fig. 2.29). The presence of the *tert*-butyl substituents impacted more the reaction. Reduced quinazolinone **198** was isolated in 33 % yield. However the major product seemed to be a dearomatized

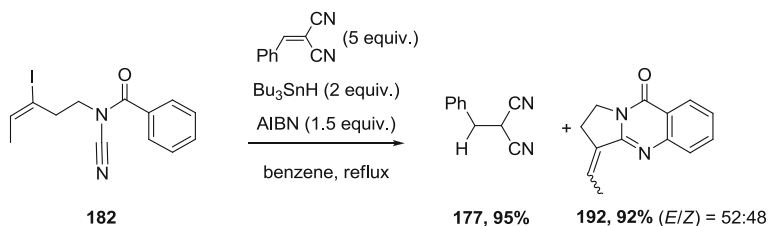


Fig. 2.28 Radical cyclization in the presence of a sacrificial acceptor

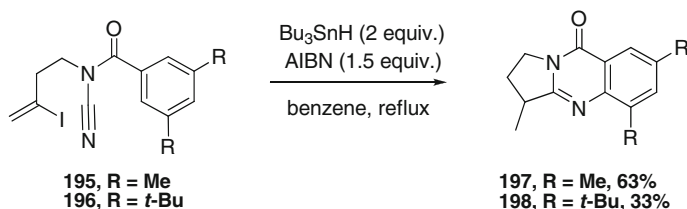


Fig. 2.29 Influence of *meta* substituents on the cascade process

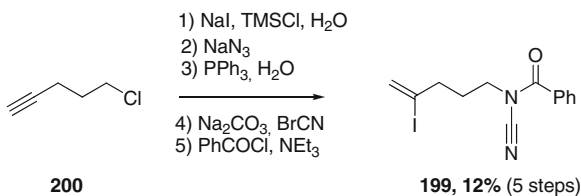
compound according to the crude NMR. Unfortunately, the several attempts we made to isolate the major product were not successful. Hence we were not able to conclude on the influence of *meta*-substituents on the H migration.

2.3.2.4 Influence of Ring Size

Finally, we wanted to investigate the influence of the size of the first ring formed. We thus decided to prepare *N*-acylcyanamide **199**, as a precursor for the synthesis of 6-6-6 tricyclic system. Compound **199** was synthesized similarly to the other precursors, in 5 steps from 5-chloropent-1-yne **200** (Fig. 2.30).

The cyclization of precursor **199** proved surprisingly inefficient, since the dehalogenated product **201** was isolated as the major product in 45 % yield (Fig. 2.31). Among the cyclized products, the two third was still bearing an *endo* double bond (**202**, 16 %) and one third had undergone the H migration (**203**, 8 %). We demonstrated previously that once in the *endo* position, the double bond can no more be reduced by the H migration. Consequently, the lower amount of

Fig. 2.30 Synthesis of the precursor of 6-6-6 tricyclic system



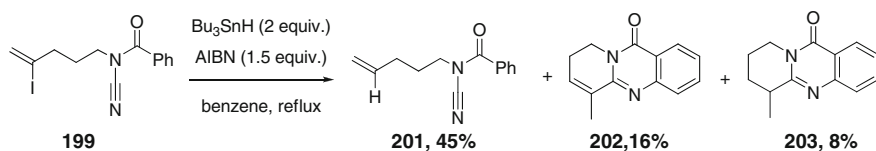


Fig. 2.31 Influence of the ring size on the cascade

reduced product might be explained by a more rapid migration of the *exo* double bond to the *endo* position in the 6-6-6 tricyclic system.

2.3.2.5 Mechanistic Proposal

According to all the experiments described previously, we propose the mechanism depicted in Fig. 2.32 for the H migration. After iodide abstraction by the tin radical, vinyl radical **204** would be formed and add to the cyanamide moiety via a 5-*exo-dig* cyclization. The amide-iminyl radical **205** generated would then be trapped by the benzoyl ring, leading to cyclohexadienyl radical **206**. Subsequently, the rearomatization would occur via bimolecular addition of “H•” on the *exo* double bond of a previously formed quinazolinone **178**. This step would generate a new molecule of quinazolinone **178** and a tertiary radical **207** that would be reduced by Bu_3SnH . This mechanistic proposal is in accordance with all the investigative experiments performed, however it has not been proven formally.

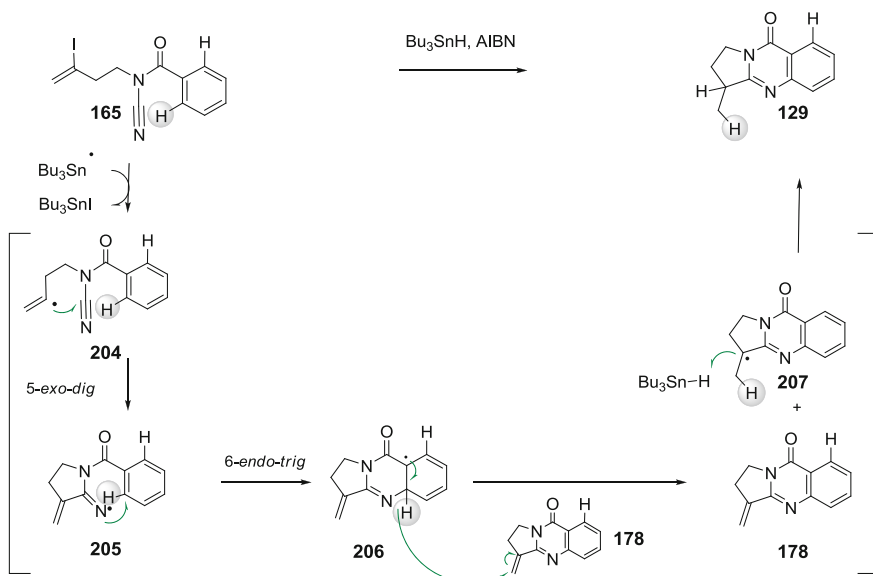


Fig. 2.32 Mechanistic proposal for the H migration

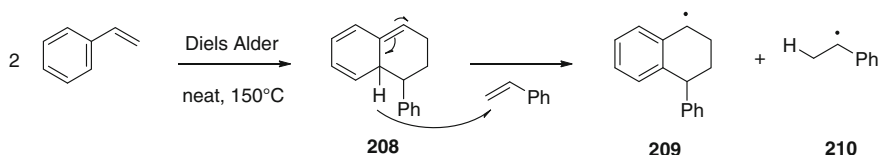


Fig. 2.33 Mayo mechanism for the autoinitiation of styrene

Deeper mechanistic studies on the kinetic of the reaction as well as DFT calculations should be performed to bring new insights into this unprecedented cascade. Alternatively, AIBN could play the role of a temporary radical trap, and the hydrogen could be first transferred to the initiator, generating AIBN(H)[•] (**103**, Fig. 2.46.) which would then deliver H[•] to the quinazolinone **178**.

The key hydrogen transfer step that we propose is reminiscent of the Mayo mechanism for the thermal autoinitiation of styrene, which has been confirmed by Rizzardo [26, 27]. In this mechanism (Fig. 2.33) two molecules of styrene undergo a Diels–Alder reaction to provide adduct **208**. This adduct then undergoes hydrogen atom transfer with a third molecule of styrene in a rearomatization step leading to benzyl radical **210** that can initiate the polymerization.

2.3.3 Migration of Carbon- or Heteroatom-Substituents

Having explored the migration of hydrogen, we envisioned to test the outcome of the cascade with precursors bearing *ortho*-substituents at the benzoyl group. As described in the bibliographical part, aromatizations with concomitant extrusion of carbon- or heteroatom- substituents have been reported. These types of processes were described either in the context of homolytic aromatic substitution or via aromatization of cyclohexadienyl radicals obtained by hydrogen abstraction. In some cases, these extruded radical could be trapped by activated olefin. We hoped that in our case, the *N*-acylcyanamide precursor could play the role of both the source of extruded radical and the trap. We would hence obtain a formal migration of substituent from the benzoyl ring to the *exo*-double bond during the cascade cyclization (Fig. 2.34).

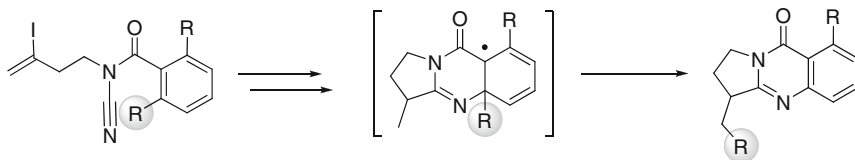


Fig. 2.34 Strategy envisioned for the migration of *ortho* substituents

2.3.3.1 Synthesis of *Ortho,Ortho'*-disubstituted Benzoyl Cyanamides

Conveniently, a set of five *ortho,ortho'*-disubstituted benzoyl cyanamides and one *ortho*-monosubstituted benzoyl cyanamide could be synthesized by reaction of common intermediate **164** with corresponding acyl chlorides. All acylations proceeded smoothly except from the reaction between cyanamide **164** and 2,4,6-triisopropylbenzoyl chloride. Probably because of the steric hindrance involved by *ortho*-substituents, this reaction was very sluggish. After stirring at room temperature during one week, 15 % of desired *N*-acylcyanamide could be isolated in one test reaction; but unfortunately, this reaction could not be reproduced at higher scale (Fig. 2.35).

2.3.3.2 Cyclization of Carbon-Substituted Benzoyl Cyanamides

When treated in the usual radical conditions, precursors **211** and **212** pleasingly afforded, in average yields, the desired quinazolinones **217** and **218** where methyl and isopropyl group respectively underwent the planned migration. Both benzene and *tert*-butanol could be used as solvent with similar efficiency. Methyl radical is not reported to be extruded with a high dissociation rate [28], and its addition to simple alkene is slow ($k = 3.3 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$ for the addition of $\text{Me}^\bullet$ to ethene at 338 K) [29]. The successful outcome of the cascade in our case could be explained by a bimolecular mechanism, and by the highly conjugated nature of the trapping olefin (Fig. 2.36).

To our great delight, the treatment of precursor **213** with Bu_3SnH and AIBN added at a rate of 0.06 mmol of $\text{Bu}_3\text{SnH/h}$ in refluxing *tert*-butanol allowed the isolation of quinazolinone **219** in 55 % yield. Running the reaction in benzene proved strongly detrimental. This could be explained by the fact that trifluoromethyl radical is known to add readily to aromatic solvents [30, 31]. The trifluoromethyl group appears in a large number of structures of interest to the pharmaceutical and agrochemical industry [32–35], and the methodologies available to generate trifluoromethyl radicals are not so numerous [36, 37].

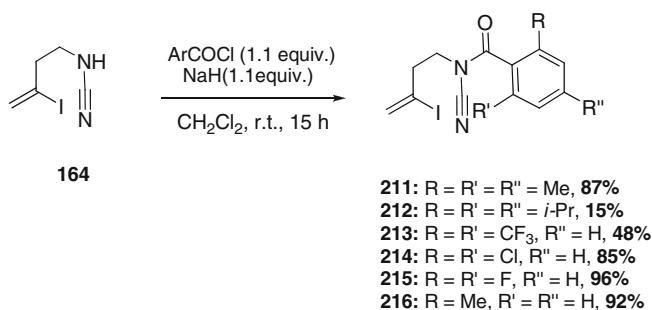


Fig. 2.35 Synthesis of *ortho*-substituted *N*-acylcyanamides

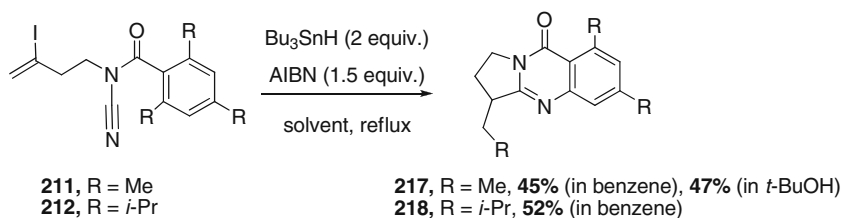


Fig. 2.36 Migration of alkyl radicals

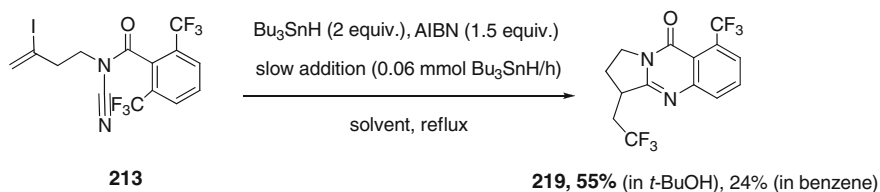


Fig. 2.37 Migration of trifluoromethyl radical

Consequently any new methodology for the generation and trapping of $\text{CF}_3^\bullet$ is of high interest (Fig. 2.37).

Trifluoromethyl radical is very electrophilic and can consequently abstract hydrogen from cyclohexane or THF. The newly formed radical can then add to activated unsaturations as demonstrated by Fuchs. He reported that treatment of vinyl triflone **220** with AIBN in THF, afforded trisubstituted olefin **221** by the chain transfer mechanism depicted in Fig. 2.38.

We decided to perform our cyclization in THF, to observe if in our conditions, trifluoromethyl radical-mediated H abstraction at THF could prevail to CF_3 migration. When only 2 equivalents of THF were introduced in the reaction mixture, the migration at quinazolinone remained the major pathway. Quinazolinone **219** was isolated in 41 % yield along with 17 % of unsaturated compound **222**. When the reaction was run in THF, the migration was completely inhibited, and olefin **222** was isolated as the sole product. These experiments seem to confirm that the migration occur via the extrusion of a trifluoromethyl radical. When THF is present as a solvent, it reduces $\text{CF}_3^\bullet$ to CF_3H , generating THF radical. This latter appears to be unable to add to the quinazolinone under our reductive condition (Fig. 2.39).

Finally, we wished to run a competition experiment between hydrogen and methyl group migration. Dissymmetric precursor **216** was cyclized under the usual conditions, leading to quinazolinone **223** as the sole isolated product (Fig. 2.40). This result could be explained by the faster radical addition at the less substituted carbon of the benzoyl ring.

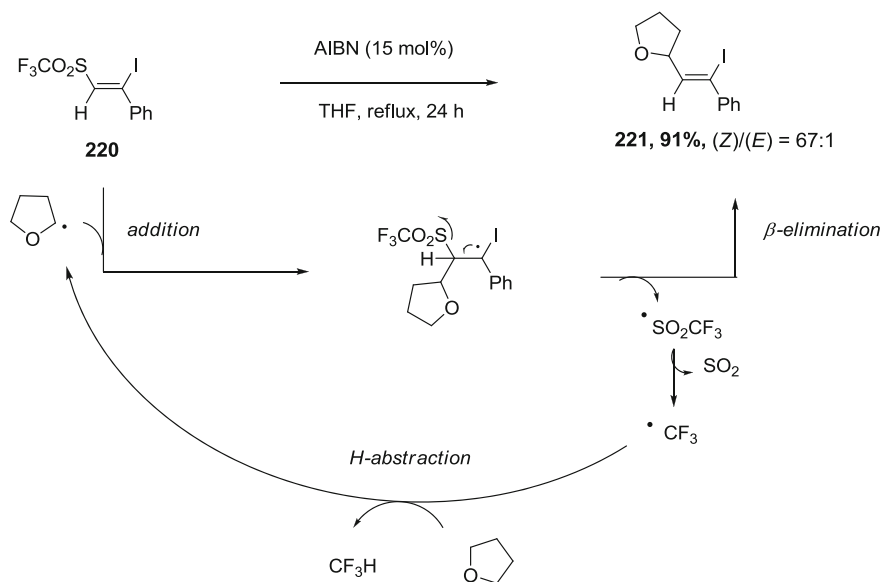


Fig. 2.38 Reaction of vinyl triflate with THF under radical initiation

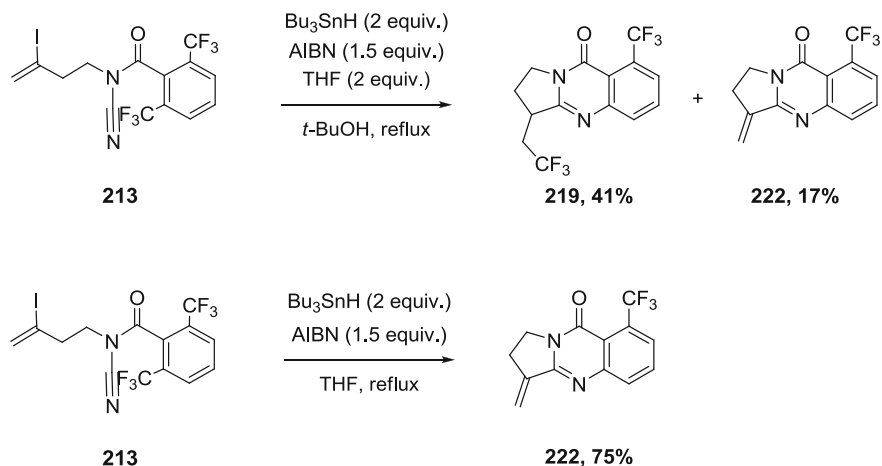
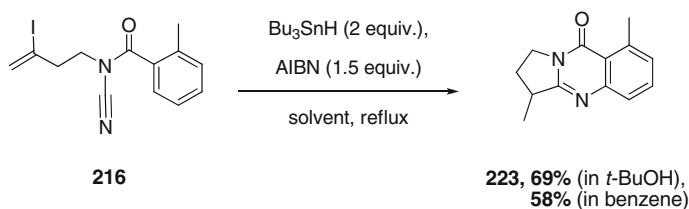


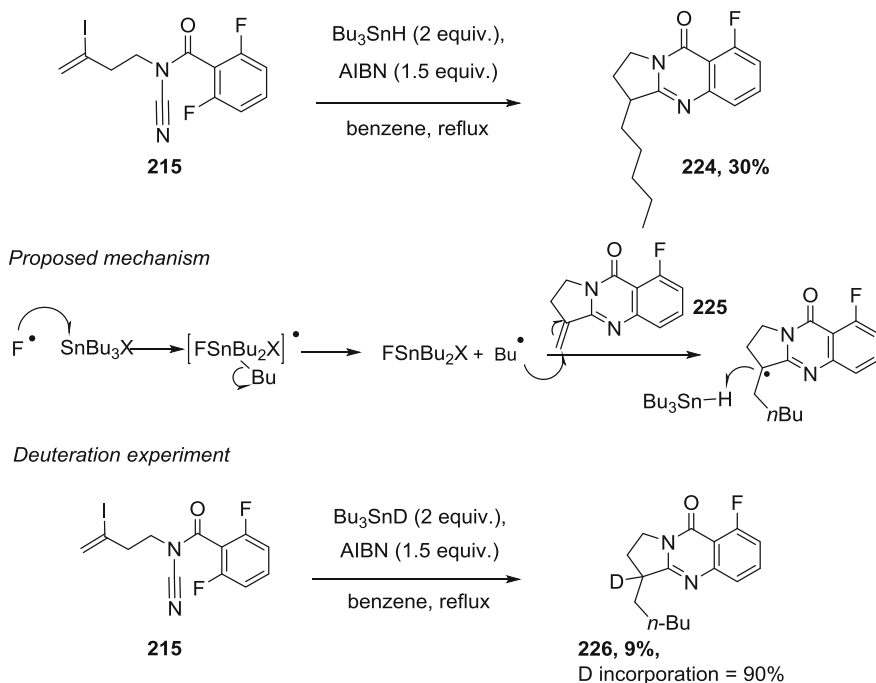
Fig. 2.39 Test of the influence of the presence of THF in our cascade

2.3.3.3 Cyclization of Heteroatom-Substituted Benzoyl Cyanamides

Heteroatom-substituted benzoyl cyanamides led to less clear results than their carbon counterparts. The cyclization of *o,o'*-dichloro precursor **214** resulted in degradation. Further studies would be necessary to understand at which step in the mechanism this degradation occurs. The cyclization of *o,o'*-difluoro precursor **215**

**Fig. 2.40** Cyclization of dissymmetric precursor

led to a complex mixture from which quinazolinone **224** could be isolated in 30 % yield. This product was very surprising, and we could imagine the mechanism depicted in Fig. 2.41 to explain its formation. Fluorine radical could be extruded during aromatization and, thanks to its high affinity for tin, add to the mediator. This addition would result in the release of butyl radical that would add to the *exo*-double bond of quinazolinone **225**. Running the reaction with Bu_3SnD indeed provided deuterated quinazolinone **226**, albeit only in 9 % yield. ^{19}F and ^{119}Sn NMR studies are currently performed to gain new insights into this unprecedented outcome. Disappointingly, running the reaction with Ph_3SnH or $(\text{TMS})_3\text{SiH}$ instead of Bu_3SnH led to inseparable complex mixtures.

**Fig. 2.41** Cyclization of difluoro precursor

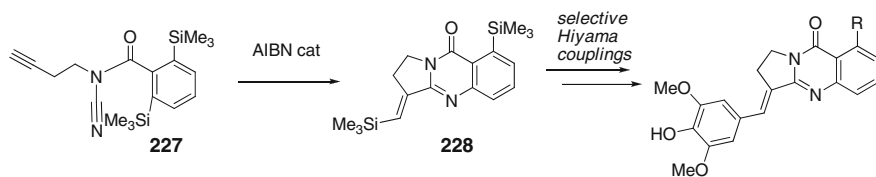


Fig. 2.42 Possible perspective involving TMS migration

To conclude, the study on the behavior of vinyl radicals in cascades with *N*-acylcyanamides allowed us to develop an original domino process, involving unexpected migrations of hydrogen or carbon substituents triggered by homolytic aromatic substitutions [38]. Careful mechanistic studies helped us to get better insights into the cascade. In a broader manner, this study brings precious elements for the better understanding of homolytic aromatic substitutions. As a perspective, many new applications to this migration could be proposed. For instance, in the aim of synthesizing isaindigotone, silylated precursor **227** could be cyclized in the presence of a catalytic amount of AIBN. Quinazolinone **228** may be obtained under those tin free conditions and transformed isaindigotone via selective Hiyama couplings (Fig. 2.42).

2.4 Addition of Nitrogen Centered Radicals

Our next challenge was to test the reactivity of nitrogen centered radicals in cascades with cyanamides. The use of aminyl radicals in cascades is challenging due to kinetic reasons. As illustrated on Fig. 2.43, the lazy amino radical has a lower cyclization rate than the corresponding alkyl radical. Even more importantly, the competition between direct reduction and cyclization is less in favor of cyclization for aminyl radicals compared to alkyl radicals [39].

Nevertheless, we were particularly interested in using aminyl radicals since we realized that their addition on cyanamide followed by homolytic aromatic substitution would provide us with a straightforward synthesis of tricyclic guanidines (Fig. 2.44).

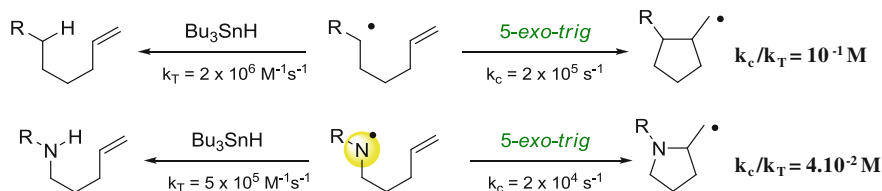
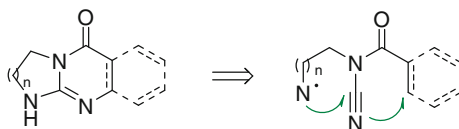


Fig. 2.43 Comparison of the kinetics of cyclization and reduction for aminyl and alkyl radicals

Fig. 2.44 Objective of the project

2.4.1 Synthetic Targets: Polycyclic Guanidines

2.4.1.1 Bioactivity

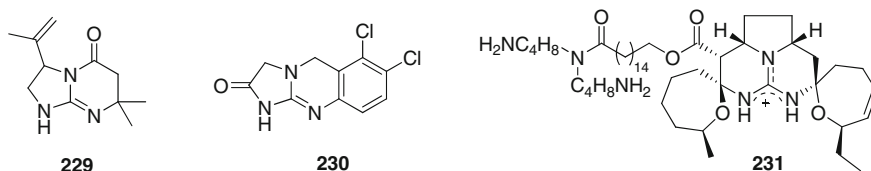
Polycyclic guanidines frameworks are found in a range of natural or bioactive products (Fig. 2.45). Hence, alchornine alkaloid **229** was isolated in 1969 from small rain-forest tree *Alchornea javanensis*; [40] anagrelide **230** is a drug used for the treatment of thrombocytosis; [41] cyclic guanidines saxitoxin, ptilocaulin and tetrodotoxin are potent ion-channel blockers and ptilomycalin A **231** is a marine alkaloid exhibiting remarkable antitumor activities [42].

2.4.1.2 Applications in Bio-inspired Molecular Recognition

In biological systems, the strong ion-pairs formed by arginine side chain with oxoanions, such as carboxylates or phosphates, are critical to stabilize protein tertiary structures. They also play a preponderant role in the interactions between proteins and carbohydrates or nucleic acids. The high affinity of the guanidinium group for oxoanions, due to its geometry and to its high pKa value (pKa ~ 12–13) allowing protonation over a wide pH range, has been extensively used in artificial receptors for molecular recognition [43]. Thus, Mendoza has reported the use of chiral guanidinium based receptor **232** for the enantioselective recognition of zwitterionic amino acids (Fig. 2.46). L-Tryptophane could be for example extracted from a racemic mixture in 40 % efficiency and 99 % *ee* thanks to the hypothetical formation of complex **233** [44].

2.4.1.3 Organocatalysis

Chiral polycyclic guanidines are promising organocatalysts for reactions that proceed through ionic transition states. Guanidines thus act as effective catalysts in

**Fig. 2.45** Natural and bioactive polycyclic guanidines

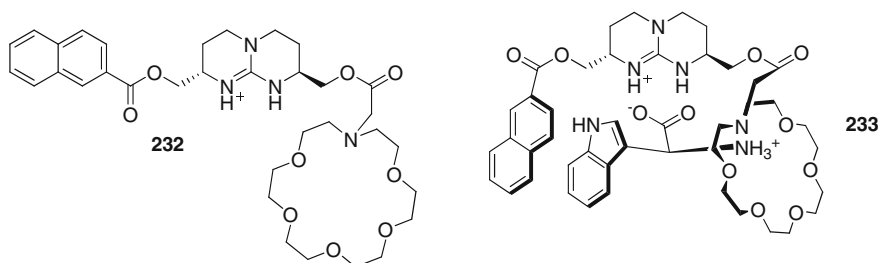


Fig. 2.46 Guanidinium based receptor for the enantioselective recognition of L-tryptophan

several highly enantioselective reactions such as base-catalyzed Diels-Alder, Strecker reaction, conjugate additions or enantioselective protonations [45]. Thus, chiral C_2 -symmetric guanidine **234** was used as a bifunctional catalyst for the enantioselective addition of HCN to *N*-benzhydrylimine **235** (Fig. 2.47) [46]. The reaction is thought to proceed via the protonation of catalyst with HCN forming a guanidinium cyanide complex that can serve as hydrogen bond donor to the imine. Pre-transition state assembly **237** then directs the attack of the cyanide at the re face of the imine.

2.4.2 Generation of Aminyl Radicals

Finding the appropriate way to generate the aminyl radical was the most challenging point of the project. N-Centered radicals can be easily obtained by homolytic cleavage of relatively weak bonds, *e.g.* N–N, N–S, N–O and N–Halogen

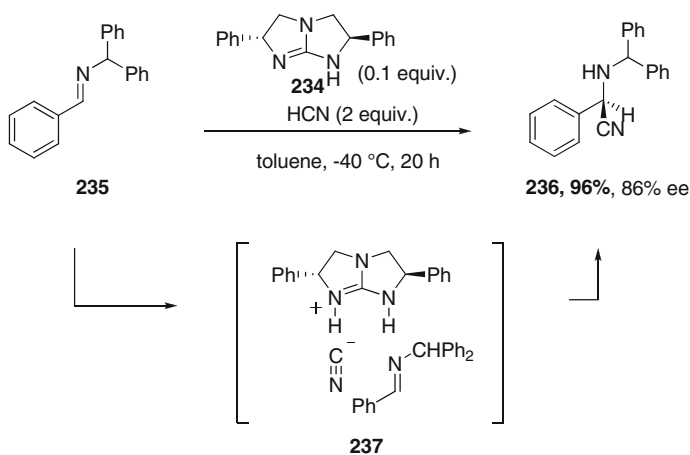


Fig. 2.47 Enantioselective Strecker reaction catalyzed by bicyclic guanidine

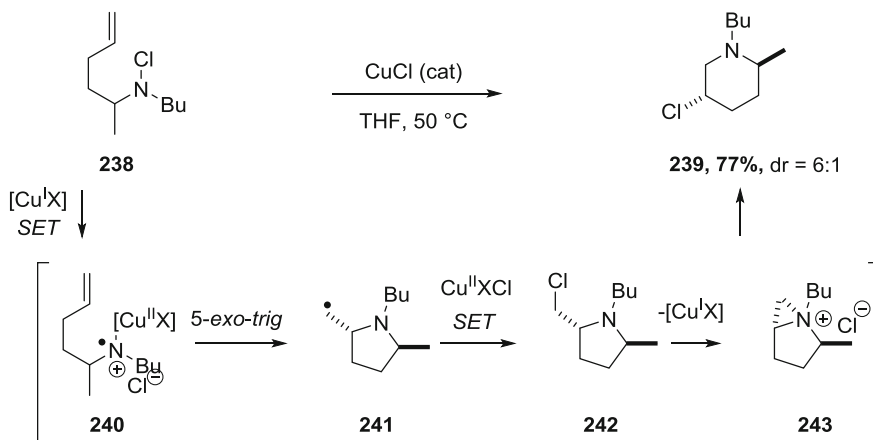


Fig. 2.48 Copper(I) mediated generation of aminyl radical from chloroamine

bonds, but also strong N–H and N–C bonds in specific conditions. This subject has been reviewed in depth by Zard in 2008 [47] and just recently by our group [48]. Only a few significant methodologies will be presented here.

2.4.2.1 Aminyl Radicals by Homolytic N-Halogen Bond Cleavage

Haloamines have been widely used as precursors since they can be conveniently prepared by electrophilic halogenation of the corresponding amines using *N*-halosuccinimides. Their major drawback is their low stability. Homolysis of the N–X bond under photochemical activation is the most widespread way to trigger the radical reaction. Nevertheless, the development of alternative catalytic reduction of haloamines with low valent metal salts allowed the generation of aminyl radicals in a more controlled fashion. Thus, *N*-chloramine **238** has been converted to piperidiny derivatives **239** in the presence of copper(I) salts (Fig. 2.48) [49]. Single electron transfer from copper (I) catalyst allows the reduction of the N–Cl bond to generate radical cation **240**. The aminyl radical undergoes a fast 5-*exo-trig* cyclization to afford pyrrolidiny intermediate **241** and release copper(II) complex. The primary alkyl radical formed reacts through a second SET process leading to the formation of the corresponding chlorinated pyrrolidine **242** and the regeneration of the catalyst. Alkyl chloride **242** finally undergoes an anionic stereoselective ring expansion to yield compound **239**.

2.4.2.2 Aminyl Radicals by N–O Bond Cleavage

N-Benzoyloxyamines such as **244** can also be reduced by copper(I) salts and undergo transfer group reactions (Fig. 2.49) [50]. Similarly to the reaction with

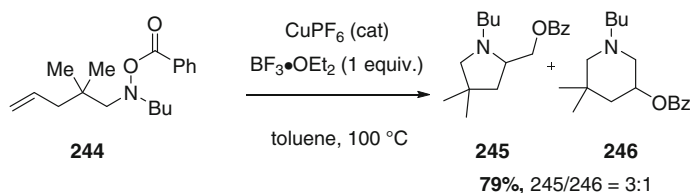


Fig. 2.49 Copper(I)-mediated generation of aminyl radical from *N*-benzoyloxyamine

haloamines, the copper(II)-benzoyl complex formed during the reduction step transfers the acyl group to the primary C-radical obtained after cyclization. This step thus allows the regeneration of the catalyst. It should be noted that no reaction was observed without Lewis acid, which indicates that the acyloxy group must be activated to weaken the N–O bond.

2.4.2.3 Aminyl Radicals by N–C Bond Cleavage

N–C Bonds are generally too strong to lead to efficient homolytic cleavage. In specific cases i.e. the release of ring strain, decarboxylation or aromatization [51], such process can nonetheless occurs. For example, irradiation of carbamate derivative of *N*-hydroxy-3-thiopyridone (*N*-PTOC) **247** in the presence of trifluoroacetic acid leads to carbonyloxy radical **248** that undergoes rapid fragmentation to release a molecule of carbon dioxide and protonated aminyl radical **249** (Fig. 2.50) [52]. This latter performs a fast 5-*exo-trig* cyclization. Finally, chain propagation is achieved by the attack of the resulting alkyl radical on thiocarbonyl

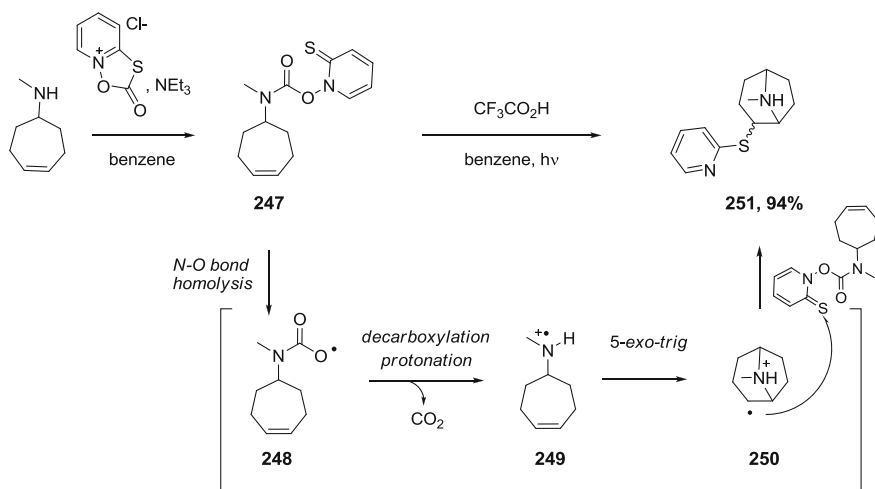


Fig. 2.50 Generation of aminyl radical from *N*-PTOC carbamate

function. The drawback of the methodology is that precursor **247** is poorly stable and must be prepared in situ.

2.4.2.4 Aminyl Radical by N–S Bond Cleavage

Sulfenamine derivatives have been successfully employed for the generation of *N*-centered radicals via homolytic substitution of tin radical at the sulfur atom. As reported by Li, treatment of *N*-(benzenesulfonyl)pent-4-enylamines **252** with the Bu₃SnH/AIBN system affords the corresponding aminyl radicals. These latter can cyclize onto the alkene moiety to provide a mixture of pyrrolidines and piperidines. The nature of the substituents of the alkene is critical for controlling the product distribution [53]. The only limitation to this methodology can be the access to the sulfenyl precursor (Fig. 2.51).

2.4.2.5 Generation of Aminyl Radicals Via N–H Bond Cleavage

Generation of aminyl radicals from tosylamines can be achieved by proton and electron transfer with oxydants such as Cu(OAc)₂. The oxidation of tosyl-*o*-allylanilines **255** has thus been reported using Cu(OAc)₂ and Cs₂CO₃ at 120 °C. As a result, aniliny radical **256** is formed and cyclizes in a 5-*exo-trig* mode [54]. The alkyl radical generated can subsequently perform a homolytic aromatic substitution. Hence, this intramolecular carboamination of alkenes could lead to straightforward synthesis of hetero-multicyclic compounds (Fig. 2.52) [55].

2.4.2.6 Generation of Aminyl Radical via N–N Bond Cleavage

Carbon- or heteroatom radicals can add at the α or γ position of the azido moiety to give 1,3- or 3,3-triazenyl radicals **259** and **260** [56]. With both aliphatic and aromatic azides, the latter fragment by loss of N₂ to form aminyl radical (Fig. 2.53).

Thus, intermolecular addition of stannyl radicals to alkyl azides provides transient nucleophilic stannylaminyl radicals. Kim was the first to prove that those radicals could cyclize onto unsaturations to form heterocyclic rings (Fig. 2.54). He

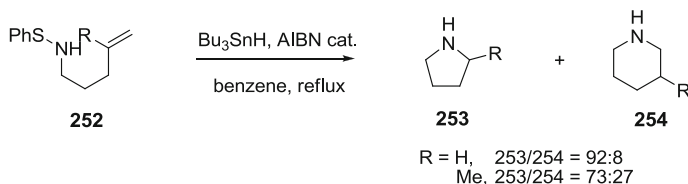


Fig. 2.51 Generation of aminyl radical via homolytic cleavage of N–S bond

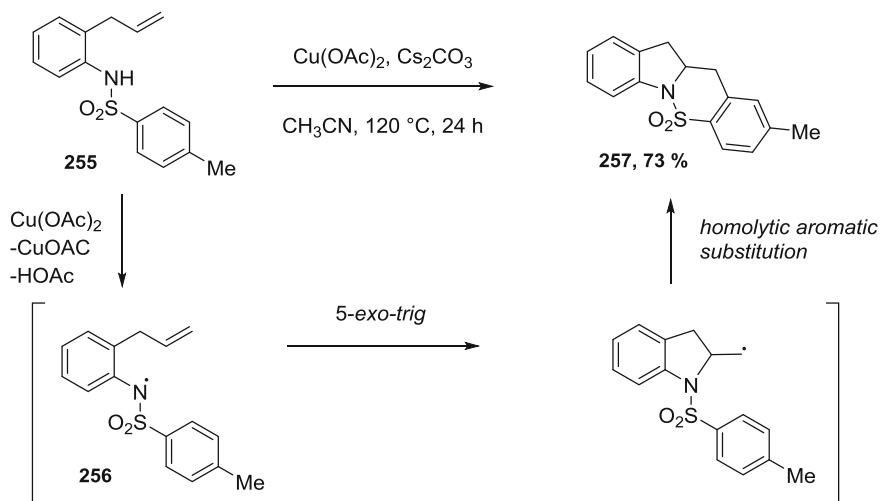


Fig. 2.52 Generation of aminyl radical via proton and electron transfer with Cu(II) salts

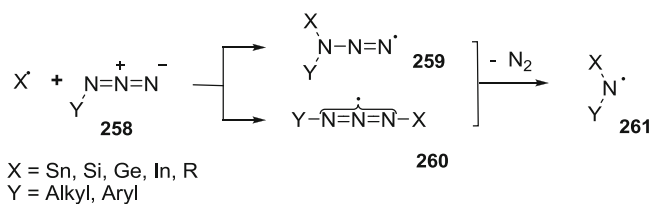


Fig. 2.53 Generation of aminyl radical by homolytic addition to azides

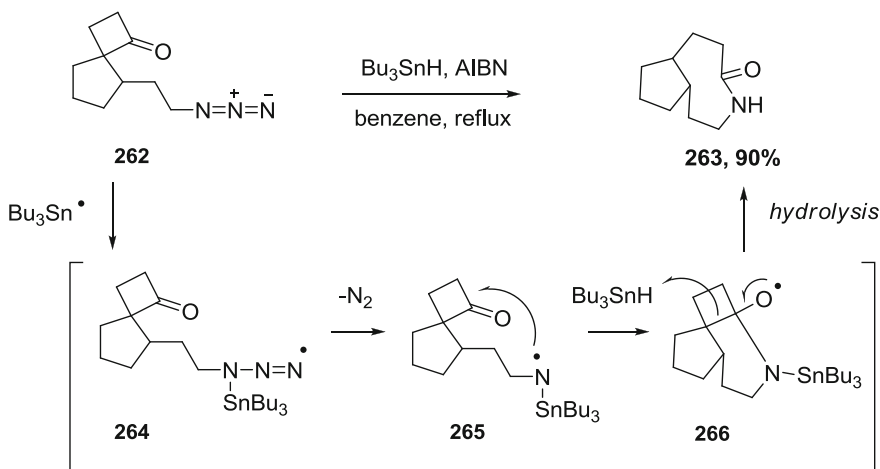


Fig. 2.54 Addition of stannylaminyl radical to carbonyl function

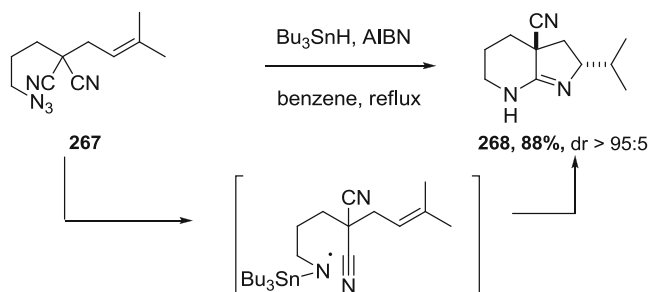


Fig. 2.55 Addition of stannylaminyl radical to nitrile group

treated azido precursor **262** with Bu_3SnH and AIBN, and generated stannylaminyl radical **265** which added to the carbonyl group. Fragmentation and subsequent hydrolysis afforded lactam **263** in 90 % yield.

Spagnolo reported subsequently that stannylaminyl radicals could add intramolecularly to electrophilic cyano groups. The generated aminoimidyl radicals could undergo further cyclizations onto suitably positioned alkenes and aromatic rings (Fig. 2.55) [57].

To decide what strategy we would use for our cascade with *N*-acylcyanamides, we took into account the synthesis of the precursor. Cyanamide functions are prone to hydrolysis under acid or basic aqueous treatment, so we wished to maintain the construction of *N*-acylcyanamide moiety as the last step of the precursor synthesis. Besides, the precursor should not bear more than one free amino group at the cyanation step to prevent polycyanation issues. These requirements oriented us towards the use of azido precursor, since azide functions are stable under a wide range of conditions, easily introduced at any step of the synthesis and cannot undergo undesired cyanation. Furthermore their use for the generation of aminyl radicals is atom economical relatively to the other methodologies, and we could be optimistic about their reactivity with cyanamides after their good behavior with nitriles.

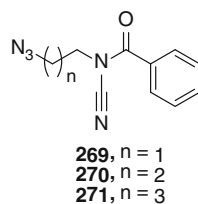
2.4.3 Synthesis of the Precursors

2.4.3.1 Variation of the Link Length Between the Azide and the Cyanamide Functions

Our first objective was to synthesize azido-*N*-acylcyanamide precursors **269–271** with increasing length of the alkyl link between the azide and the cyanamide functions (Fig. 2.56).

Precursors **269** and **270** were prepared similarly starting from bromoalkylamines hydrobromide **135** and **138** (Fig. 2.57). Nucleophilic substitution with sodium azide in H_2O afforded, after basic treatment, azidoamines **272** and **273** that

Fig. 2.56 Precursors with variable chain lengths



underwent subsequently cyanation and acylation. The synthesis of the *N*-acyl cyanamides was thus very rapid, the only difficulty being related to the volatility of the intermediates.

Precursor **271** was prepared starting from 1,4-dibromobutane **274** (Fig. 2.58). Double nucleophilic substitution with sodium azide in DMF afforded 1,4-diazaibutane **275**. An efficient mono-Staudinger reduction to azido amine **276** was then achieved in biphasic conditions using triphenyl phosphine in Et₂O/EtOAc/5 % HCl aqueous solution [58]. In these conditions, as soon as the azidoamine is formed, it is protonated by HCl and migrates to the aqueous layer, thus preventing over-reduction to diamine. Subsequent cyanation and acylation afforded the desired *N*-acylcyanamide precursor **271**.

2.4.3.2 Variation of the Substituents on the Alkyl Chain Linking Azide and Cyanamide Functions

Next, we endeavored to prepare precursors diversely substituted on the alkyl chain. We decided to prepare precursor **277–279** starting from the corresponding amino alcohols (Fig. 2.59).

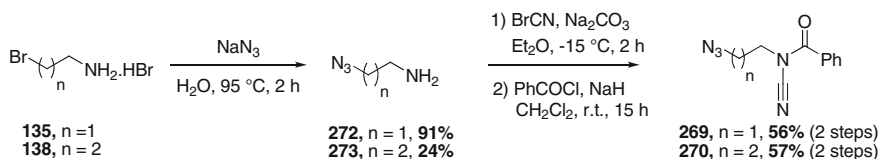


Fig. 2.57 Synthesis of *N*-acylcyanamides 269 and 270

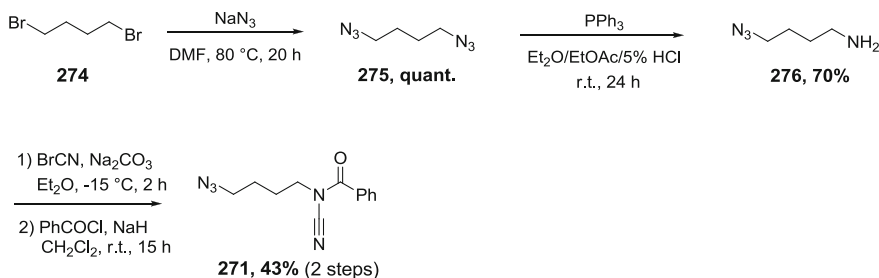
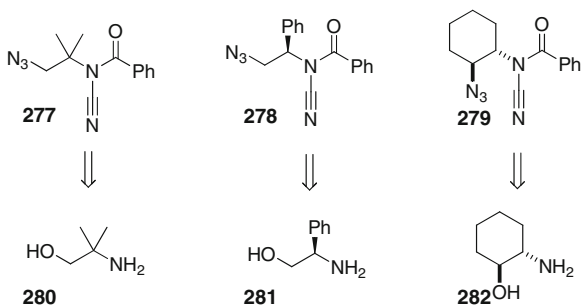


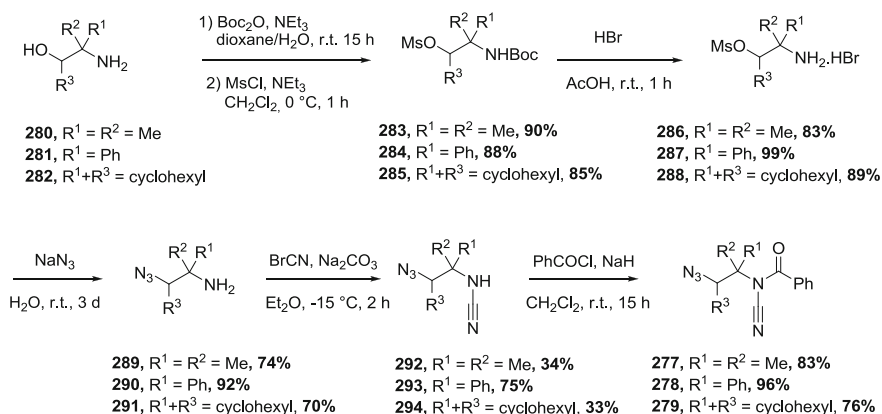
Fig. 2.58 Synthesis of *N*-acylcyanamide precursor 271

Fig. 2.59 Precursors with various substituents on the alkyl chain

N-protection of **280–282** with Boc group gave protected amino alcohols which were subsequently mesylated to **283–285** [59]. Deprotection with HBr as a 2 M solution in acetic acid allowed the isolation of amino mesylates **286–288** as their hydrobromide salts. The protonation of the amine conveniently prevents intramolecular nucleophilic substitution. Conversion of mesylates into azides **289–291** was achieved by treatment with sodium azide in water. Final cyanations and acylations afforded the desired precursors (Fig. 2.60).

2.4.3.3 Variation of the Benzoyl ring

In order to check the scope and limitations of the cascade, we sought to prepare precursors **295–299** bearing different types of substituents on their benzoyl ring, as well as heteroaryl rings. We treated cyanamide **293**, with various acyl chlorides in the presence of sodium hydride and obtained the corresponding *N*-acylcyanamides with medium to good yields (Fig. 2.61).

**Fig. 2.60** Synthesis of *N*-acylcyanamides 277–279

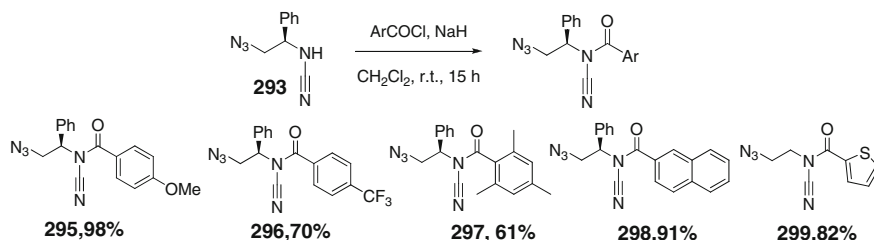


Fig. 2.61 Synthesis of precursors with various aryl traps

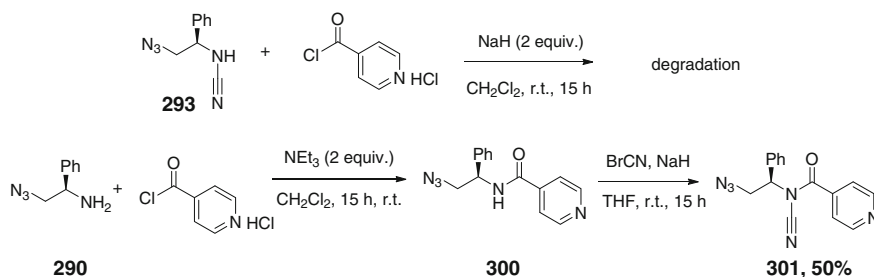


Fig. 2.62 Synthesis of isonicotinoyl precursor

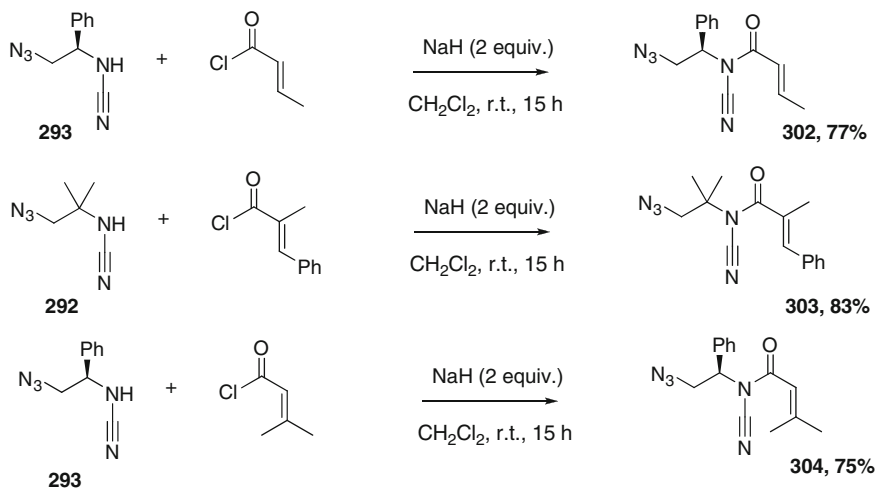
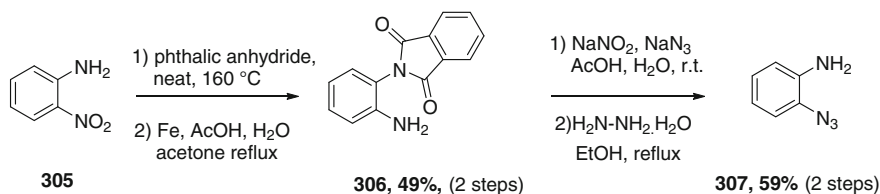
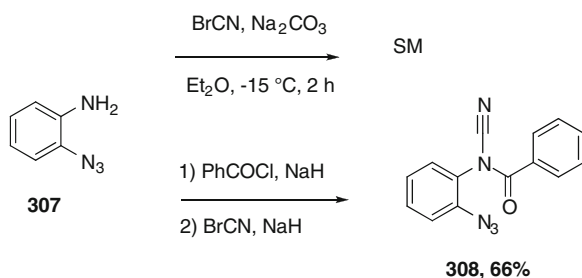
Treatment of cyanamide **293** with isonicotinoyl chloride hydrochloride led only to degradation (Fig. 2.62). Fortunately, inverting the acylation and the cyanation steps allowed us to isolate the desired isonicotinoyl precursor **300** successfully.

Finally, the final aryl acceptor was replaced with olefins. Precursors **302**, **303** and **304** bearing substituted double bonds could be synthesized starting from the corresponding cyanamides and acyl chlorides (Fig. 2.63).

2.4.3.4 Synthesis of Aryl Azide Precursor

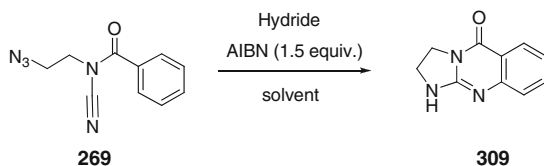
Finally we decided to test a precursor with an aryl azide function. Starting from 2-nitro aniline **305**, 2-azido aniline **307** was conveniently obtained by a 5 steps procedure reported by Hall [60]. This procedure involved first the protection of the amino group by conversion to phthalimide, followed by the reduction of the nitro group with iron and acetic acid. Diazotization of the amino group followed by treatment of the diazonium with sodium azide then afforded the 2-phthalimidophenyl azide. This latter was finally deprotected by treatment with hydrazine in methanol to give 2-azidoaniline **307** (Fig. 2.64).

Two strategies for the preparation of the *N*-acylcyanamide **398** were then tested. Direct cyanation of the aryl amine by treatment with BrCN and Na_2CO_3 was not successful. However, an acylation/cyanation sequence allowed us to obtain the desired precursor **308** incorporating aryl azide and *N*-acylcyanamide functions (Fig. 2.65).

**Fig. 2.63** Synthesis of precursors with olefins as acceptors**Fig. 2.64** Synthesis of 2-azido amine**Fig. 2.65** Synthesis of aryl azide precursor

2.4.4 Optimization of Guanidine Radical Synthesis

The simplest substrate **269** was selected to test the feasibility of the cascade and optimize the radical conditions (Fig. 2.66). The first set of conditions we used were the one developed for the cyclization of vinylcyanamides, i.e. treatment with



Entry	Solvent, Temp.	Addition rate (mmol/h)	Hydride (equiv.)	Additives	Yield 399 [%]
1	benzene, reflux	0.2	Bu ₃ SnH (2)	-	41
2	toluene, reflux	0.2	Bu ₃ SnH (2)	-	30
3	<i>t</i> -BuOH, reflux	0.2	Bu ₃ SnH (2)	-	31
4	benzene, reflux	one batch	Bu ₃ SnH (2)	-	20
5	benzene, reflux	0.06	Bu ₃ SnH (2)	-	76
6	benzene, reflux	0.06	Bu ₃ SnH (1.2)	-	43
7	benzene, reflux	0.06	(TMS) ₃ SiH (2)	-	<10
8	benzene, reflux	0.06	Bu ₃ SnH (2)	BF ₃ ·Et ₂ O (1 equiv.)	38
9	benzene, 50°C	0.06	Bu ₃ SnH (2)	-	25
10	benzene, r.t.	0.06	Bu ₃ SnH (2)	Irradiation	<10
11	benzene, r.t.	0.06	Bu ₃ SnH (2)	BEt ₃ , air, no AIBN	<10

Fig. 2.66 Optimization of the radical cyclization of azidocyanamide 269

Bu₃SnH (2 equivalents) and AIBN (1.5 equivalents) slowly added (0.2 mmol Bu₃SnH/h) in refluxing benzene. To our great delight, guanidine **309** could be isolated after silica gel column chromatography in 41 % yield (entry 1). A rapid solvent screening showed that replacing benzene with *t*-BuOH or toluene led to reduced yields (entries 2,3). We then investigated the influence of the rate of addition of Bu₃SnH (entries 4,5). Addition in one batch resulted in poor isolated yield of 20 %, while slower addition (0.06 mmol Bu₃SnH/h) allowed us to obtain the desired guanidine in 76 % yield. We then sought to reduce the amount of Bu₃SnH to 1.2 equivalents (entry 6) or to replace it with (TMS)₃SiH as a mediator (entry 7) but both attempts proved detrimental for the conversion and consequently for the yield. Several Lewis acids were tested in the idea of improving the cyclization of the aminyl radical. Indeed, kinetic studies have demonstrated that Lewis acids activate aminyl radicals towards cyclizations by increasing their rate constants more by 3 orders of magnitude. One of the most efficient Lewis acid was reported to be BF₃ [61]. In our case, the addition of Lewis acids resulted in a decrease in the yield of final product (entry 8), possibly because of the presence of multiple sites of complexation in the *N*-acylcyanamide precursor. We finally tried to reduce the temperature of the reaction which resulted in a progressive drop of the yield (entries 9–11). Two types of initiations at room temperature were tested: AIBN under irradiation and BEt₃ with O₂, but they both led to less than 50 % conversion and less than 10 % yield of desired guanidine. The major side product was uncyclized aminocyanamide. We consequently conserved the conditions of entry 5 as our best conditions.

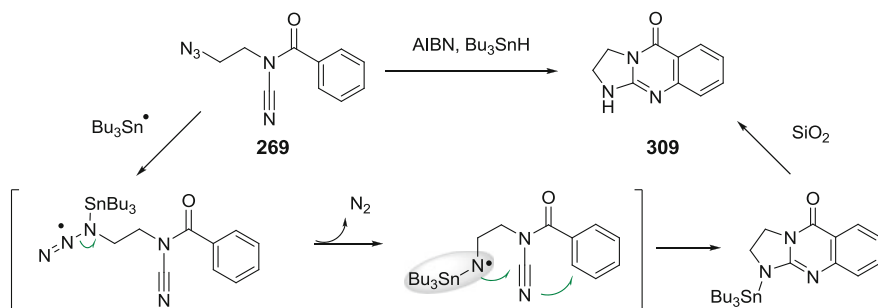


Fig. 2.67 Proposed mechanism for the radical synthesis of guanidines

We think that the cascade proceeds as depicted in Fig. 2.67. Addition of tin radical to the azide function leads after loss of nitrogen to a nucleophilic stannylaminyl radical that can cyclize on the cyanamide moiety. The resulting amide iminyl radical performs a homolytic aromatic substitution at the benzoyl ring, leading to stannylated guanidine. Silica gel chromatography finally allows the isolation of the free guanidine **309**.

2.4.5 Scope of the Guanidine Synthesis

With our optimized conditions in hands, we examined the scope of our methodology. We first investigated the influence of the length and substitution of the alkyl chain on the outcome of the reaction (Fig. 2.68). Cyclization of precursors **270** and **271** showed that increasing the number of carbons between the azide and the cyanamide function led to a progressive decrease of the efficiency of the reaction. This trend seems logical owing to the slower kinetics of 6-*exo-dig* and 7-*exo-dig* cyclizations compared to 5-*exo-dig*. This explanation was confirmed by the observation of uncyclized amino cyanamides as side products. Furthermore, the cyclization of precursor **271** can be prevented by competitive 1,5-hydrogen transfer. On the other hand, the substitution on the alkyl chain did not seem to have a strong impact on the cascade, and all the 5,6,6-tricyclic guanidines derived from precursors **280–282** were obtained in good yields.

Next, we investigated the influence of variations on the benzoyl ring thanks to the cyclization of precursors **295–301** (Fig. 2.69). Overall, our radical cascade proved rather general. The introduction of *para* substituents on the aryl ring, either electron donor or electron withdrawing groups, did not affect the efficiency of the radical cascade. Thus, precursors **295** and **296** delivered the desired guanidines **315** and **316** with the same 82 % yield. Naphtyl derivative **298** and pyridyl **301** cyclized successfully, yielding the corresponding polyheterocyclic guanidines **318** and **320** in 81 and 71 % yield respectively. The thiophene ring could also serve as final radical trap but proved more fragile under our reaction conditions. The

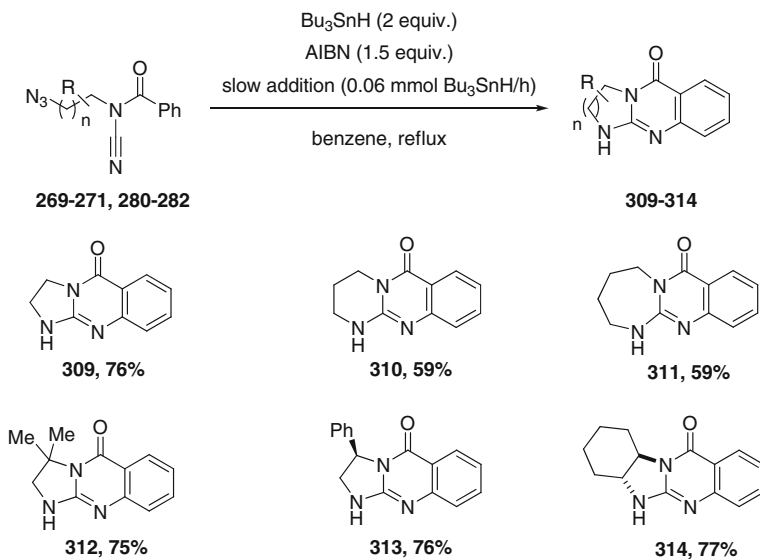


Fig. 2.68 Scope 1 of the guanidine synthesis

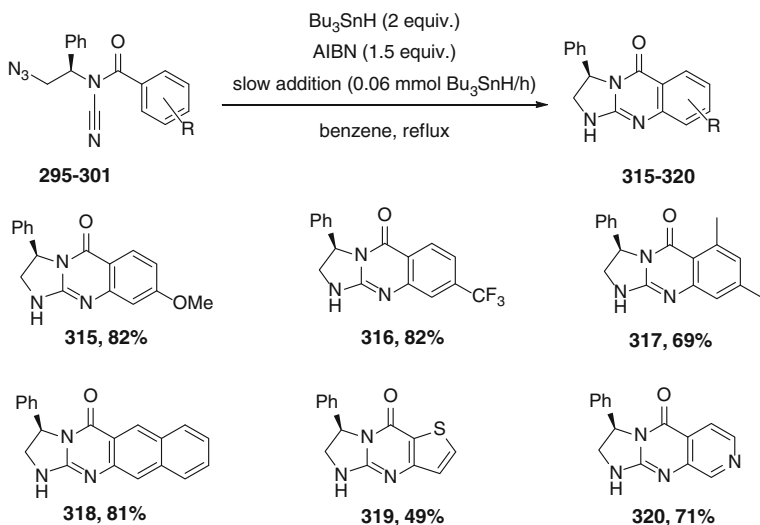


Fig. 2.69 Scope 2 of the guanidine synthesis

corresponding guanidine **319** was only isolated in 49 % yield, and the crude NMR showed that some degradation had occurred during the cyclization. Finally, the cascade could also end with the extrusion of a methyl radical, as demonstrated by the formation of desmethyl adduct **317** from precursor **299**.

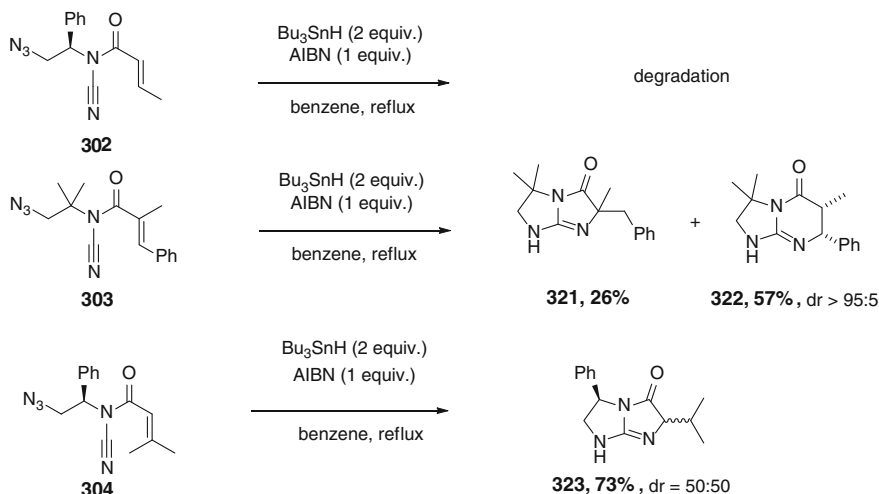


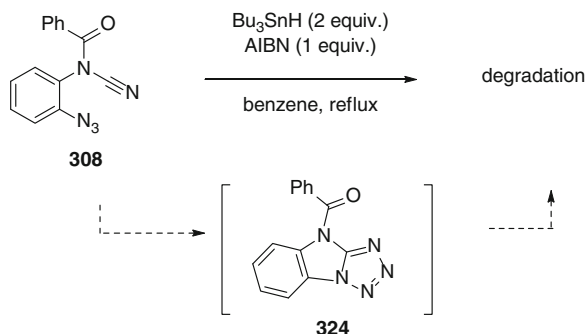
Fig. 2.70 Cyclization of *N*-enoyl cyanamides

Subsequently, we examined the possibility of replacing the final aryl acceptor with an olefin (Fig. 2.70). Cyclization of precursor **302** bearing a disubstituted activated double bond afforded mainly degradation. The stability of the precursors in our reaction conditions seemed to be highly influenced by the substitution patterns of the olefins, since when we used precursor **303** bearing a trisubstituted double bond, the cascade occurs cleanly. Two bicyclic guanidines were isolated **321** (26 %) showing a 5,5 framework arising from final 5-*exo-trig* cyclization and **322** (57 %) possessing a 5,6 framework arising from final 6-*endo-trig* cyclization followed by a diastereoselective hydrogen transfer. Precursor **304** behaved equally well and allowed us to obtain selectively the 5-*exo-trig* final cyclization, delivering guanidine **323** in 73 % yield.

Finally, we tested the cyclization of arylazide precursor **308**. Unfortunately only degradation was observed in our previous conditions (Fig. 2.71). One explanation could be that aryl azides have been reported to undergo [3+2] cycloadditions with cyanamides at only 60 °C (the temperature required for the same reactions with alkyl cyanamides are >130 °C) [62]. The corresponding tetrazoles are besides known to be unstable when they are substituted with electron withdrawing group, which would be the case with our precursor. Heating **308** in refluxing benzene could thus possibly lead to tetrazole **324** that would further decompose. In order to extend our methodology to aryl azide, we consequently have to develop conditions which allow an efficient cascade at room temperature. Liu has recently developed a methodology for the generation of aminyl radical by visible light triggered reduction of arylazide under $\text{Ru}(\text{bpy})_3$ catalysis, at room temperature [63]. We plan to test these mild conditions for the cyclization of **308**.

To conclude, we reported the first radical synthesis of cyanamides, which was achieved via addition of aminyl radicals on cyanamides as starting point of a

Fig. 2.71 Attempt to cyclize aryl azide precursor



radical cascade [64]. Most of the bicyclic and tricyclic guanidines we have synthesized have not been described previously and might possess interesting biological properties as DNA intercalating agents for example. We are currently trying to find collaborations to have them tested.

As perspectives, owing to the wide scope of products accessible via our methodology, we could try to design new chiral organocatalysts; even if the reduction of the carbonyl function present in our guanidines would probably be a prerequisite to employ them as chiral bases. The development of an intermolecular version of this reaction, starting from an azide and a *N*-acylcyanamide would allow a huge extension of the scope and should also be studied. Finally, we can envisage testing the reactivity of heteroatom-centered radicals with cyanamides, such as sulfur, silicon or phosphorous radicals.

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